PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 11013.2-304	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2008/064471	International filing date *(day/month/year)* 22 May 2008 (22.05.2008)	Priority date *(day/month/year)* 22 May 2007 (22.05.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CYPRESS BIOSCIENCE, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 24 November 2009 (24.11.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	21 AUG 2008
Applicant's or agent's file reference 2207111-WO0	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/64471	22 May 2008 (22.05.2008)	22 May 2007 (22.05.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 9/22 (2008.04)
USPC - 424/468

Applicant CYPRESS BIOSCIENCE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	15 August 2008 (15.08.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/64471

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/64471

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	6, 7	YES
	Claims	1-5, 8, 9	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1- 5, 8 and 9 lack novelty under PCT Article 33(2) as being anticipated by US 2007/0072946 A1 to Rao et al (hereinafter Rao).

Regarding claim 1, Rao discloses a method of improving physical function in fibromyalgia said method comprising administering to a patient in need thereof a therapeutically effective amount of an NSRI (para [0006], [0023], [0025], [0080]).

Regarding claim 2, Rao discloses wherein the NSRI is milnacipran, or a pharmaceutically acceptable salt thereof (para [0025]).

Regarding claim 3, Rao discloses wherein about 100 mg/day of milnacipran, or a pharmaceutically acceptable salt thereof, is administered to the patient (para [0026]).

Regarding claim 4, Rao discloses wherein about 200 mg/day of milnacipran, or a pharmaceutically acceptable salt thereof, is administered to the patient (para [0026]).

Regarding claim 5, Rao discloses wherein the milnacipran, or a pharmaceutically acceptable salt thereof, is administered in divided doses (para [0045]).

Regarding claim 8, Rao discloses further comprising adjunctively administering a second active compound for the treatment of cognitive dysfunction associated with FMS, wherein the second active compound is selected from the group consisting of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, anantiepileptic drug, a beta blocker, a sedative, a hypnotic, and combinations thereof (para [0042]).

Regarding claim 9, Rao discloses wherein the second active compound is selected from the group consisting ofmodafinil, gabapentin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, valium, trazodone , trazodone, caffeine, nicergoline, bifemelane, propranolol, atenolol, and combinations thereof (para [0042]).

Claims 6 and 7 lack an inventive step under PCT Article 33(3) as being obvious over Rao.

Regarding claim 6, as previously set forth in claim 3, Rao discloses administration of 100mg milnacipran DQ. Rao also discloses dosage ranges from 25 mg to 400 mg QD (para [0026], [0037]), as well as an indication of better results with smaller doses spread over the course of the day (i.e. twice per day) (para [0045]). While Rao does not specifically disclose wherein the milnacipran, or a pharmaceutically acceptable salt thereof, is administered as a 50 mg dose twice per day, it would, nonetheless have been obvious to one skilled in the art to administer smaller doses of milnacipran to total the QD mg prescription (such as 100mg broken into smaller doses), to enhance the effective treatment results and mitigate side-effects associated with larger, individual doses.

Regarding claim 7, as previously set forth in claim 4, Rao discloses a 200 mg QD treatment regimen of milnacipran. Also, as previously set forth in claim 6, it would have been obvious to one skilled in the art to spread the prescribed QD mg amount into smaller doses over the course of the day. Thus, while Rao does not specifically disclose wherein the milnacipran, or a pharmaceutically acceptable salt thereof, is administered as a 50 mg dose four times per day, it would have been obvious to one skilled in the art to administer the 200 mg QD prescription into smaller, 50 mg doses over the course of the day, to enhance the effective treatment results and mitigate side-effects associated with larger, individual doses.

Claims 1-9 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.